A United Kingdom Register study of in-hospital outcomes of patients receiving extracorporeal carbon dioxide removal (ECCO2R)

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DOI:
10.1177/1751143717739816

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Title: A United Kingdom Register study of in-hospital outcomes of patients receiving extracorporeal carbon dioxide removal ($ECCO_2R$)

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Disclaimers/conflicts of interest:

Daniel F McAuley and James McNamee: NIHR HTA funding (13/143/02) and NI HSC RDD funding to undertake a clinical trial of ECCO2R with in kind contribution from ALung Technologies, Inc. Nicholas A Barrett: No personal financial conflicts of interest. Educational and research funding from Maquet, Drager, Fisher & Paykel, Mitsubishi Tanabe Pharmaceuticals, Corpak, ALung Technologies.

Funding: University of Birmingham staff working on the study received funding support from NICE. NHS England provided funding to support ELSO register database modifications and ICU registration.

Keywords: intensive care; extra corporeal carbon dioxide membrane removal; mortality, complications

Summary (150 words)

Introduction Extracorporeal membrane carbon dioxide removal ($ECCO_2R$) may have a role in treatment of patients with hypercapnic respiratory failure and refractory hypoxaemia and/or hypercapnia.

Methods We report on the use, outcomes and complications in United Kingdom intensive care units reporting patients on the Extracorporal Life Support Organisation (ELSO) register.

Results Of 60 patients, 42 (70%) had primarily hypoxic respiratory failure and 18 (30%) primarily hypercapnic respiratory failure. Use of veno-venous procedures increased compared to arterio-venous procedures. Following $ECCO_2R$, ventilatory and blood gas parameters improved at 24 hours. 27 (45%) of patients died before ICU discharge, while 27 (45%) of patients were discharged alive. The most common complications related to thrombosis or haemorrhage.

Discussion There is limited use of $ECCO_2R$ in UK clinical practice and outcomes reflect variability in indications and the technology used. Usage is likely to increase with the availability of new, simpler, technology. Further high quality evidence is needed.

Introduction

Acute respiratory failure is a life-threatening condition where the respiratory system's function of oxygenation and/or elimination of carbon dioxide is inadequate, resulting in abnormally low levels of oxygen in the blood (hypoxaemia, i.e. arterial oxygen partial pressure [PaO_2] <8.00kPa) and/or abnormally high carbon dioxide levels in the blood (hypercapnia, i.e. arterial carbon dioxide partial pressure [$PaCO_2$] >6.00kPa). Hypercapnic respiratory failure may be associated with mild hypoxaemia as found in exacerbations of severe chronic obstructive pulmonary disease (COPD) or with significant hypoxaemia in conditions such as acute respiratory distress syndrome (ARDS) resulting from pathology including pneumonia, sepsis and chest trauma. Patients are often treated with non-invasive ventilation (NIV), which delivers ventilatory support via the patient's upper airway through a mask interface. For conditions such as COPD, NIV has been demonstrated to prevent the need for mechanical ventilation involving endotracheal intubation, and its complications including lung injury [1]. Rescue therapy has traditionally been invasive mechanical ventilation: this can be a life saving intervention for acute respiratory failure, but despite optimal lung protective ventilation, refractory hypoxaemia and/or hypercapnia may result in some patients. There is a small body of literature describing a role for extracorporeal membrane carbon dioxide removal ($ECCO_2R$) in this circumstance [2]. Other developing roles for $ECCO_2R$ include the facilitation of better lung protective ventilation in patients with ARDS as an adjunct to mechanical ventilation [3].

Extracorporeal membrane oxygenation (ECMO) and more recently extracorporeal membrane carbon dioxide removal ($ECCO_2R$) are techniques that can provide additional and alternative respiratory support for patients using specifically designed membrane gas exchangers derived from cardiac bypass technology for extracorporeal blood flow. When used for respiratory failure, veno-venous ECMO requires high blood flow rates (3-6L/minute) to provide full respiratory support for patients to enable both adequate oxygenation and carbon dioxide (CO_2) clearance. However when CO_2 clearance alone is required, much lower blood flows are required. CO_2 clearance is determined by multiple factors, including the carriage of CO_2 in the blood (dissolved, as bicarbonate and as carbamino compounds),

the gradient between the venous partial pressure of CO_2 and the sweep gas CO_2, sweep gas flow rate, pH, haemoglobin and the efficiency of the gas exchange membrane. From a clinical perspective, CO_2 removal will occur and can be manipulated by alteration in the sweep gas flow rate, which is analogous to minute ventilation in the native lung [4]. As long as a concentration gradient across the membrane is maintained with adequate fresh gas flow, $ECCO_2R$ may be performed with much lower blood flows which enable limited oxygenation but can achieve substantial CO_2 clearance. This supplementary, or partial, CO_2 clearance effectively allows for reduced minute ventilation by the native lungs. It is possible that this approach may benefit patients with COPD by avoiding mechanical ventilation and allow improved lung protective ventilation in patients with ARDS. The aim is to supplement native pulmonary CO_2 clearance, either to allow a reduction in mechanical ventilator settings with the intention of limiting ventilator induced lung injury in conditions such as ARDS [3,5] or to avoid intubation/facilitate early extubation in patients with conditions such as COPD.

The circuit of the $ECCO_2R$ systems can use either arteriovenous (AV) or veno-venous (VV) configuration. AV-$ECCO_2R$ drains blood from the patient's arterial system through a femoral arterial line and returns it to the femoral vein, effectively creating an artificial arteriovenous shunt. Consequently AV-$ECCO_2R$ relies upon the patient's circulation and does not require a pump as arterial blood pressure maintains blood flow continuously through the circuit and is returned through the vein. VV-$ECCO_2R$ uses a dual lumen cannula to access blood and a centrifugal pump to drive the blood through the gas exchange membrane and is conceptually similar to renal replacement therapy widely used in critical care. AV-$ECCO_2R$ has an intrinsic risk of arterial injury which may be avoided using the VV technique. Systemic anticoagulation is preferred and recommended but not essential for both AV and VV $ECCO_2R$.

A high quality systematic review [6] on the use of $ECCO_2R$ for acute respiratory failure secondary to acute respiratory distress syndrome included two randomised control trials (RCTs) [7,8] and 12 observational studies with AV and VV $ECCO_2R$ used in seven studies each. Neither RCT showed a significant difference with respect to mortality although in the

more recent RCT of low flow VV ECCO2R ventilator free days at 28 and 60 days were increased only in the more hypoxaemic subgroup with partial pressure of inspired oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <20 kPa. Complication rates ranged from 0-25%, the most common complication with AV $ECCO_2R$ being lower limb ischaemia secondary to arterial cannulation. Other adverse events included compartment syndrome and one lower limb amputation. In VV $ECCO_2R$, clotting within the circuit was the most common complication. A further systematic review of the use of $ECCO_2R$ in exacerbations of COPD included 10 studies at high risk of biased reporting on 87 patients. In 65 out of 70 patients intubation was avoided with the use of $ECCO_2R$. Eight out 11 major complications were bleeding episodes with one venous perforation at the catheter site, one pneumothorax and a retroperitoneal bleed secondary to iliac artery perforation [9].

National Institute for Health and Care Excellence (NICE) guidance [10] recommends that $ECCO_2R$ should only be used in patients with potentially reversible hypercapnic respiratory failure or those being considered for lung transplantation; the procedure should only be undertaken with special arrangements for clinical governance, consent and audit or research, because the evidence on the safety of $ECCO_2R$ showed a number of well-recognised complications, and evidence on its efficacy was limited in quality and quantity.

A UK survey of Intensive Care Units (ICUs) was carried out with the support of the Intensive Care Society, yielding information on UK clinical practice [11]. Out of 141 ICUs (57% response rate), 47 (33%) had used $ECCO_2R$, although many had used it infrequently (median 2 patients). The most common indications were pneumonia and asthma, but $ECCO_2R$ had also been used for a number of other indications including in patients with ARDS from non-respiratory sepsis and trauma, in COPD, as a bridge to lung transplant. AV-$ECCO_2R$ was more frequently used but more complications were reported. The use of VV-$ECCO_2R$ as a newer technology was reported to have increased. The survey indicated $ECCO_2R$ uptake in UK ICUs is characterised by sporadic use for a range of indications.

NICE commissioned the Birmingham and Brunel Consortium External Assessment Centre to facilitate clinical data collection by clinicians caring for patients receiving $ECCO_2R$ in the UK

by working with the Extracorporeal Life Support Organization (ELSO) registry. The collection of UK $ECCO_2R$ patient data in the ELSO register provides an opportunity to consider outcomes including safety in a UK cohort of patients.

Methods

Aim

To report on the use, outcomes and complications of $ECCO_2R$.

Design

Observational study of ICU patients undergoing $ECCO_2R$

Setting

UK ICUs.

Recruitment of centres

The ELSO register dataset was edited to allow the recording of $ECCO_2R$ procedures and outcomes including procedure related adverse events by ELSO members. ICUs that were not already full members of ELSO were identified in 2013 through a survey[11]. An associate membership category was introduced to enable UK ICUs that were not full members (these are centres providing ECMO or cardiac extracorporeal support) to register patients receiving $ECCO_2R$. Hospital Episode Statistics (HES) data, manufacturer data and reported use were cross-tabulated to inform the process of contacting centres while recognising that HES data had some limitations in that data were available only retrospectively and, although the $ECCO_2R$ procedure was recorded, relevant procedures may have been misclassified. ICUs were contacted a second time via email and if needed were telephoned in the summer of 2014 when registration and input of patient data were once again encouraged as appropriate. A further round of targeted email and telephone follow-up of centres that may have had cases was undertaken at the beginning of 2015. A request for anonymised data

for research purposes was made to ELSO and a final anonymous dataset was produced in June 2015.

The study was carried out under the pre-existing arrangements for clinical governance and agreements between contributing centres and the ELSO register.

Statistical considerations

The co-primary efficacy and safety outcomes of interest were: discharged home or transferred alive from the hospital offering $ECCO_2R$ and adverse events including procedure related complications. Pre-specified adverse events of interest were lower limb ischaemia (including compartment syndrome and amputation), arterial, venous and device thrombus formation, plasma leakage, vascular access damage and bleeding complications.

Other outcomes of interest were pre-$ECCO_2R$ blood gases and ventilator settings compared with those 24 hour post application.

AV and VV $ECCO_2R$ were predefined subgroups. Although diagnostic information was included in the ELSO register, the indication for using $ECCO_2R$ was not explicitly stated in the ELSO registry. Therefore based on the limited dataset available and taking into account ventilator settings, blood gases and haemodynamics prior to $ECCO_2R$ to derive a consensus opinion, four independent ICU clinicians retrospectively assessed if patients primarily received $ECCO_2R$ to manage hypercapnia or to manage the consequences of hypoxia by enabling lung protective ventilation.

Pre-specified subgroups by indication were Acute Respiratory Distress Syndrome (ARDS), asthma and chronic obstructive pulmonary disease (COPD). The rationale for subgroup selection was as follows: ARDS is the indication most reported; however use of $ECCO_2R$ in asthma has been reported in the UK; and there are trials registered to evaluate its use in severe exacerbations of COPD. In practice, however, the reported indications did not fit easily into unique subgroups or reporting was constrained by group size and therefore these subgroups have not been reported below.

Given that this was an observational register, no formal sample size calculation was carried out prior to data collection. Statistical analysis is descriptive, with statistical tests having only been performed for pre-specified subgroups where data were sufficient. Tests were appropriate to the population distribution of the relevant variables and where appropriate exact methods and non-parametric tests were used.

Ethical approval and consent to participate

The purpose of the ELSO registry is to provide member institutions data to improve quality of care to patients but data may also be requested by members for research purposes. Data are submitted as a limited de-identified dataset. Given purpose of the register is to collect data for quality improvement and anonymous data are collected, individual patient consent for data entry into the register is not sought. Approval for this study using anonymized data was obtained from the Science, Technology, Engineering and Mathematics Ethical Review Committee of the University of Birmingham (reference ERN_15-0556) prior to the request for research data from ELSO.

Results

ELSO supplied an anonymised download of data on 60 patients registered as having received $ECCO_2R$ in UK hospitals on 11.6.2015.

Patient characteristics and clinical course pre-$ECCO_2R$

Patient characteristics and pre-$ECCO_2R$ support are described in Table 1. 78% of patients were specified as having received conventional ventilator support while 2 (3%) patients received high frequency oscillatory ventilation with the mode of ventilation not specified for the remainder. The median time from admission to $ECCO_2R$ treatment was 96 hours (interquartile range 18 to 30 hours, n=58), and the median time from intubation to $ECCO_2R$ was 48 hours (interquartile range 24 to 202 hours, n=51).

Of the 42 (70.0%) patients considered to have a primarily hypoxic presentation, 24 (57.1%) had pneumonia, 5 patients septic shock, 2 were specified as having acute respiratory failure

without further qualification, 2 influenza and 8 other underlying diagnoses. Of the 18 patients considered to be primarily hypercapnic, 5 had COPD, 3 pneumonia, 2 pneumothorax, 2 asthma and 6 other underlying diagnoses.

Pre-$ECCO_2R$ history

22 patients (36.7%), were not recorded as receiving any specific organ support prior to $ECCO_2R$, while 18 had one organ support coded, 7 had 2 and 13 more than 2. The most common organ support recorded was vasopressor/inotropic drugs (Table 1).

Three patients suffered a cardiac arrest prior to being commenced on $ECCO_2R$. One had asthma requiring manual hand ventilation and was eventually discharged alive. One patient had a nutritional/metabolic cardiomyopathy and asthma, another parainfluenza virus pneumonia and both subsequently died despite recovery from respiratory failure. A further patient with bronchiectasis had $ECCO_2R$ as a bridge to lung transplant also died despite recovery from respiratory failure. One patient with cerebral oedema also required manual hand ventilation.

$ECCO_2R$ treatment and outcomes

$ECCO_2R$ treatment characteristics are described in Table 2 below. Arterio-venous (AV) $ECCO_2R$ predated veno-venous $ECCO_2R$, with VV-$ECCO_2R$ becoming the most prevalent once this technology became available (Figure 1).

Patients receiving VV $ECCO_2R$ had relatively fewer hours of $ECCO_2R$. The median duration and interquartile range of hours on $ECCO_2R$ treatment were 192 (108-324) for AV (n=17) and 120 (95-208) for VV (n=38) (Mann-Whitney test not statistically significant).

Blood flow rate at four and 24 hours was only recorded for three patients receiving AV $ECCO_2R$. Where the flow rate unit was recorded in ml/minute, this was converted to L/minute except for one patient where the incorrect unit of measurement seemed to have been recorded. The median and interquartile range at four hours (n=40) for VV-$ECCO_2R$

was 0.47 L/min (0.40 to 1.15) and at 24 hours (n=38) was also 0.47 L/min (0.42 to 1.13) (Wilcoxon test not statistically significant). Cannulation is described in Table 3.

When ventilation parameter settings were compared, taking those during the worst ABG values in the six hours prior to $ECCO_2R$ and those at the best ABG value at 24 hours following application of $ECCO_2R$, all ventilation settings were shown to have been reduced (Table 2). Median $PaCO_2$ was reduced with a concomitant improvement in median pH.

27/60 (45%) patients were discharged from the hospital alive. Of the 27/60 (45%) patients who died in the course of the procedure, 21 had multi-organ failure, four as having diagnosis incompatible with life and two following family requests. 33 (55%) patients survived $ECCO_2R$ but a further 6/60 (10%) died prior to discharge from the $ECCO_2R$ centre. Overall survival to discharge rate of 45%. 13 patients, 48.1% of those discharged alive, were discharged home. 9 out of 22 patients receiving AV $ECCO_2R$ and 18 out of 38 patients receiving VV $ECCO_2R$ were discharged alive (p=.907). 20/42 (47.6%) of hypoxic patients compared with 13/18 (72.2%) hypercapnic patients survived the procedure (p=0.428) and 17/42 (40.5%) compared with 10/18 (55.6%) were discharged alive (p=0.141). Age, hours of $ECCO_2R$ treatment, time from intubation to $ECCO_2R$, worst $PaCO_2$ in the 6 hours before $ECCO_2R$, worst PaO_2 in the 6 hours before discharge, worst pH in the 6 hours before discharge and time from admission to ECCO2R were not associated with death before discharge (Mann Whitney test). 10 women (40.0%) compared with 23 men (65.7%) died before discharge (p=0.087).

19 patients (31.7%) experienced complications (Table 4), with 11 having 1 complication, 2 having 2, 3 having 3, 2 having 4 and 1 having 7. 15 patients (39.5%) of those receiving VV ECCO2R and 4 (23.5%) of those receiving AV ECCO2R had 1 or more complication. 3 patients receiving AV ECCO2R and 4 receiving VV ECCO2R had cannulation site bleeding.

Discussion

This observational study of patients of patients undergoing $ECCO_2R$ treatment in the UK reported to the ELSO registry displays considerable clinical heterogeneity which may be

reflected in the mixed outcomes at discharge. While ICUs were actively encouraged to register patients, complete population coverage was not achieved, in part reflecting unanticipated use of $ECCO_2R$ for a single patient in many centres. Findings reflect changes in practice over time. Use of $ECCO_2R$ in a veno-venous configuration is increasing in respect to arterio-venous, advances in the technology and its perceived relative safety. In this series it appears that the procedure is used in some patient groups to manage hypercapnia and in others, primarily hypoxic patients, to facilitate lung protective ventilation. $ECCO_2R$ showed some success in reducing $PaCO_2$ and ventilator settings with the potential for lung protection, though only limited evidence of efficacy can be provided by a register study. $ECCO_2R$ has been used in a relatively sick patient cohort: only 45% left hospital alive. As only a small number of patients received high frequency oscillatory ventilation it was not possible to specifically look at this subgroup.

Complication rates were higher than previously reported in a systematic review[5] but mechanical complications were relatively infrequent, with cannulation site bleeding being the most frequent procedure related adverse event. Assessment of whether other reported complications are procedure related is problematic, given the complexity of the included patients' condition. Interpretation is difficult, given changing technology and experience: ECMO requires larger cannulae and no arterial puncture is required for veno-venous $ECCO_2R$. In contrast to earlier studies, lower limb ischaemia, compartment syndrome and amputation were not reported: this may be related to increasing experience and use of veno-venous technology. Given the sporadic use of the procedure in many centres and patient heterogeneity, further multicentre observational studies to capture procedure related adverse events and patient outcome, ideally linked to national audit data, would be of value.

Survival in this relatively sick cohort is within the range reported for observational studies of $ECCO_2R$ in ARDS. There are insufficient patients in the study to confirm a difference in outcomes based on hypoxaemia vs hypercapnia though the data might be considered to support the conclusion that $ECCO_2R$ enables a reduction in mechanical ventilation requirement in this group of patients. Evidence on comparative effectiveness from

randomised control trials in well characterised patient cohorts is needed. Ongoing trials such as the National Institute of Health Research Health Technology Assessment funded trial of protective ventilation with veno-venous lung assist in patients with acute hypoxic respiratory failure (REST trial; ISRCTN31262122) and an ongoing trial in exacerbations of COPD (NCT02086084) should inform the effectiveness of $ECCO_2R$.

Acknowledgements

We gratefully acknowledge the assistance of the Extracorporeal Life Support Organisation (ELSO) and of Peter Rycus in carrying out this study. We are also grateful for the support of the Intensive Care Foundation. We would like to thank all of the Intensive Care Units who contributed patients to this study and members of the Steering Committee. Amanda Chapman, Joanna Long, Samantha Burn, George Bramley, Zulian Liu and Melita Shirley organized and carried out the ICU surveys with assistance from Susie Campbell and Matthew Bentham and were funded by NICE. NHS England provided funding to support ELSO register database modifications and ICU registration.

Declaration of conflicting interests

Daniel F McAuley and James McNamee: NIHR HTA funding (13/143/02) and NI HSC RDD funding to undertake a clinical trial of ECCO2R with in kind contribution from ALung Technologies, Inc. Nicholas A Barrett: No personal financial conflicts of interest. Educational and research funding from Maquet, Drager, Fisher & Paykel, Mitsubishi Tanabe Pharmaceuticals, Corpak, ALung Technologies.

Funding acknowledgement

University of Birmingham staff working on the study received funding support from NICE. NHS England provided funding to support ELSO register database modifications and ICU registration.

Availability of supporting data

The data that support the findings of this study are available from the Extra Corporeal Life Support Organisation (ELSO) but restrictions apply to the availability of these data, which were used under license for the current study in line with ELSO Data Use Agreements, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Extra Corporeal Life Support Organisation.

Authors' contributions

CC contributed to the conception and design of the study, performed statistical analyses and contributed to the interpretation of data, and drafted the manuscript. NB, an ELSO steering committee member, requested anonymised data for research purposes from ELSO. AB, NB, D McA, J McN and HP contributed to the conception and design of the study, the interpretation of data and revision of the manuscript. AB, NB, DMcA and JMcN assessed the primary purpose of ECCOR in each patient, providing a consensus opinion. All authors have read and approved the final version of the manuscript.

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Figure 1: Mode of $ECCO_2R$ by treatment year

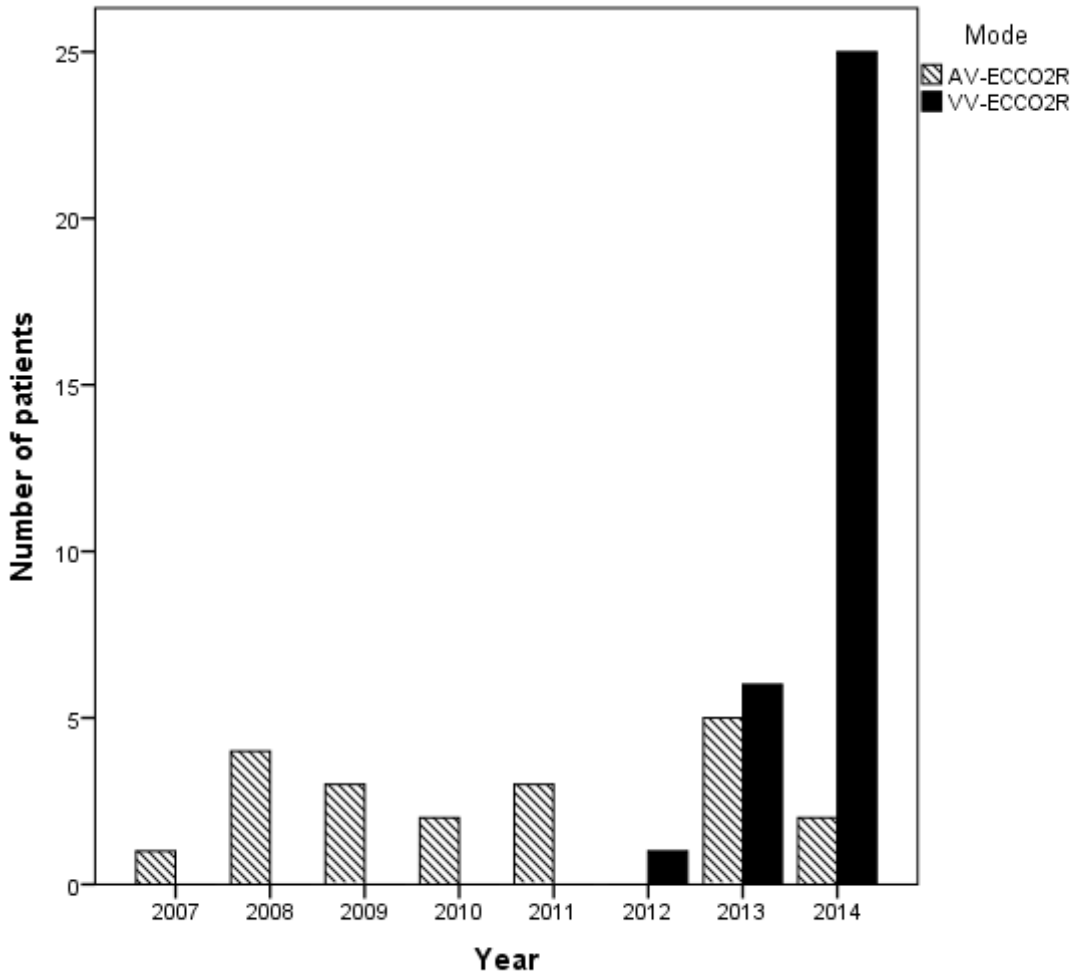

Table 1: Patient characteristics and pre-$ECCO_2R$ support

	Median	Interquartile range	Minimum	Maximum
Age (n=60)	58	46-68	24	78
	n	%		
Male	35	58.3		
Female	25	41.7		
White	54	90.0		
Asian	3	5.8		
Black	1	1.7		
Other	2	3.4		
Hypoxic	42	70.0		
Hypercapnic	18	30.0		
Ventilatory support:				
Conventional	47	78.3		
High frequency oscillatory ventilation	2	3.3		
Unknown	11	18.3		
Vasopressor/inotropic drugs	25	41.7		
Norepinephrine	13	22.8		
Neuromuscular blockers	11	19.3		
Steroids	8	13.3		
Narcotics	5	8.3		
Nitric oxide	2	3.5		
Epinephrine	1	1.8		
Milrinone	1	1.8		

Table 2: Ventilator settings, blood gases and haemodynamics pre-$ECCO_2R$ and at 24 hours of $ECCO_2R$

		Worst values in 6 hours pre-$ECCO_2R$				Best values at 24 hours of $ECCO_2R$					
	n	Medi-an	inter-quartile range	min.	max.	n	median	inter-quartile range	min.	max.	p (Wilcoxon)
Rate/Hz	37	22	17.0-28.0	4	42	36	18	14-24	8	38	.002
Mean airway pressure	21	16	9-27	5	35	21	15	10-23	5	37	.033
FiO_2	54	.70	.50-.90	.21	1.00	.53	.55	.38-.70	.21	1.00	<.000
Peak inspiratory pressure/ Amplitude	49	30	26.0-33.25	18	72	45	24	20-28	8	74	<.000
Positive end-expiratory pressure	46	8	5.0-12.0	0	20	43	10	5-12	1	20	0.032
pH	55	7.1	7.1-7.3	6.8	7.6	55	7.4	7.3-7.4	7.2	7.5	<.001
$PaCO_2$ (kPa)	55	11.4	9.0-14.0	3.9	17.0	55	7.0	6.1-8.0	4.3	11.0	<.001
PaO_2 (kPa)	54	10.5	9.0-13.0	3.6	20.1	55	9.3	8.1-10.7	3.2	17.0	<.004
PaO_2 (kPa) /FiO2	52	.17	.12-.23	.05	.48	52	.17	.14-.24	.05	.57	0.555
Systolic blood pressure	39	110	96 -130	64	207	39	123	110-135	83	168	.043
Diastolic blood pressure	39	57	52-73	42	125	39	60	55-70	40	95	.980
Mean arterial pressure	35	72	67-95	52	141	35	84	73-95	61	122	.301

Table 3: Cannulation

	n
Mode:	
AV	22
Cannulation *(where specified)*:	
Left femoral vein/Left femoral artery	3
Left femoral vein/Right femoral artery	4
Right femoral vein/Left femoral artery	14
Unspecified	1
VV	38
Cannulation *(where specified)*:	
Left Internal Jugular Vein	2
Right Femoral Vein	10
Right Internal Jugular Vein	10
Unspecified	16

Table 4: Complications

	n	% of patients
Mechanical:		
Gas exchange membrane failure	1	1.7
Pump malfunction	2	3.3
Clots: oxygenator	1	1.7
Clots: other	2	3.3
Cannula problems	1	1.7s
	7	11.7
Haemorrhagic:		
GI haemorrhage	1	1.7
Cannulation site bleeding	7	11.7
Hemolysis (plasma free Hb > 50 mg/dl)	1	1.7
Surgical site bleeding	1	1.7
	10	16.7
Neurologic:		
Seizures: EEG determined	1	1.7
CNS haemorrhage by US/CT	1	1.7
	2	3.3
Renal:		
Creatinine 1.5 - 3.0	1	1.7
Haemofiltration required	5	8.3
	6	10.0
Cardiovascular:		
Inotropes	4	6.7
Cardiac arrhythmia	2	3.3
	6	10.0
Other:		
Pneumothorax requiring treatment	1	1.7
Culture proven infection	5	8.3
pH < 7.20	1	1.7
Hyperbilirubinemia (> 2 direct or > 15 total)	1	1.7

Abbreviations: GI gastrointestinal, EEG electroencephalogram, CNS central nervous system, US ultrasound, CT computed tomography.